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Research report

Modulation of morphine-induced antinociception by ibogaine and noribogaine

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Abstract

The potential modulation of morphine antinociception by the putative anti-addictive agent ibogaine and its active metabolite (noribogaine) was investigated in rats with the radiant heat tail-flick test. Ibogaine pretreatment (40 mg/kg, i.p., 19 h) significantly decreased morphine (4 mg/kg, s.c.) antinociception, with no effects in the absence of morphine. However, co-administration of ibogaine (1–40 mg/kg, i.p.) and morphine (4 mg/kg, s.c.) exhibited a dose-dependent enhancement of morphine antinociception. Co-administration of noribogaine (40 mg/kg, i.p.) and morphine also resulted in an increase in morphine antinociception, while noribogaine pretreatment (19 h) had no effect on morphine antinociception. The results show that ibogaine acutely potentiates morphine antinociception and that noribogaine could be the active metabolite responsible for this effect. However, the inhibitory effects of a 19 h ibogaine pretreatment, which resemble ibogaine-induced inhibition of morphine's stimulant properties, cannot be accounted for by noribogaine.

Keywords: Morphine; Antinociception; Ibogaine; Noribogaine

1. Introduction

Ibogaine, an indole alkaloid of the West African shrub *Tabernanthe iboga*, has gained popularity for its potential anti-addictive properties. In 1985 and 1986 two U.S. patents (patent numbers: 4 499 096 and 4 487 243) described the potential efficacy of ibogaine in treating opiate and stimulant addiction.

Opiates produce a variety of effects including euphoria, analgesia, stimulation, sedation, and addiction. The stimulant properties of opiates are evident in rats as increased locomotor activity, while the euphoric and addictive (reinforcing) properties are modeled in animal studies of opiate self-administration and place preference conditioning (e.g., [9,14]). Dopaminergic systems have been studied extensively and have been implicated as the neurochemical pathways responsible for both the stimulant and reinforcing effects of opiates (e.g., [4,16]).

Ibogaine dose-dependently decreased self-administra-

tion of intravenous morphine in female, Sprague–Dawley rats 1 h and, to a lesser but significant extent, a day later [9]. Ibogaine injected 19 h prior to morphine decreased morphine-induced locomotor activity in rats over a wide range of morphine doses (0.5–20 mg/kg, i.p.) [11]. Furthermore, ibogaine was reported to modify extracellular levels of dopamine and dopamine metabolites in various regions of the brain [10], possibly accounting for ibogaine's behavioral effects.

The impact of ibogaine on other opiate actions has not been adequately investigated. Of particular interest is the effect of ibogaine on opiate analgesia. Two studies with mice suggest that ibogaine potentiates morphine-induced antinociception [5,15]. Thus, according to the literature, its effects on the stimulant and reinforcing properties of morphine (i.e., inhibition of locomotor activity and self-administration) seem opposed to ibogaine's effect on morphine analgesia (i.e., potentiation of morphine antinociception). It is not clear whether these differences reflect differences in time-course, dose, species, or mechanism of action. The present experiments have investigated the effects of ibogaine and an active metabolite of ibogaine (noribogaine) [8,12] on morphine-induced antinociception in rats.

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2. Materials and methods

2.1. Subjects

Male, Sprague–Dawley rats (Taconic Farms Inc., Germantown, NY) weighing 250–300 g at the time of testing were used for all studies. They were housed in groups of 3–4 under normal laboratory conditions with food and water ad lib and were maintained on a normal light-cycle (lights on 07:00, lights off 19:00).

2.2. Drug solutions

Ibogaine HCl (Sigma Chemical Co., St. Louis, MO) was dissolved in sterile water to achieve a 10 mg/ml concentration by sonication of the ibogaine solution for 20 min. Solutions of noribogaine HCl (NIDA, Bethesda, MD) were prepared in the same way. Morphine sulfate was dissolved in sterile saline to a final concentration of 4 mg/ml. All drug doses are expressed as the salts.

2.3. Nociceptive testing

Nociceptive testing was performed by the radiant heat tail flick test [2]. Each animal was loosely secured by wrapping in a laboratory pad, and a box housing a projector bulb (300 W, secured under a 5.6 mm diameter hole) was positioned under the tail such that an area 2 to 5 cm from the tip rests over the light source. The test is initiated by applying approximately 40 V to the bulb (through a potentiometer), and the latency until the tail moves is recorded. Baseline scores are between 3.0 and 4.0 s, corresponding to a threshold tail temperature of about 43°C. The heat source was not adjusted between subjects. In all cases, a cut-off value of 15 s was used.

2.4. Test and injection procedure

Ibogaine-morphine interactions were investigated in two types of experiments: (1) 19 h pre-treatments with ibogaine derivatives, and (2) co-administration experiments.

For the pre-treatment experiments, animals were tested for baseline nociception by three tail-flick tests (taken at 1 min intervals) and received ibogaine (40 mg/kg, i.p.) or water vehicle. Eighteen and one half h later, animals were re-tested for baseline responses with 3 additional tail-flick tests. At the conclusion of the third test, rats were injected with morphine (4 mg/kg, s.c., neck) or saline vehicle. Nociceptive testing, with single tail-flick tests, was then repeated at times 30, 60, 90, and 120 min after morphine. Using different groups of naive rats, the same experiment was repeated with noribogaine being substituted for ibogaine.

For co-administration experiments, animals were tested for baseline nociception with 3 tests at 1 min intervals and then received ibogaine (1–40 mg/kg, i.p.) or vehicle

(water). This was immediately followed by administration of morphine (4 mg/kg, s.c., neck) or saline vehicle. Nociceptive testing was then repeated at times 30, 60, 90, and 120 min after morphine. This experiment was also performed with noribogaine.

2.5. Data analysis

The antinociceptive score of each animal was calculated as a maximum percent effect (%MPE), where

$$\%MPE = \frac{\text{Morphine latency} - \text{baseline latency}}{\text{cut-off latency} - \text{baseline latency}} \times 100$$

Individual %MPE scores were calculated for each post-morphine time. For 19 h experiments, the third post-ibogaine/noribogaine tail-flick latency was taken as the baseline score for each subject. For co-administration experiments, the third tail-flick latency was used as the baseline score.

Cut-off latencies were 15 s. %MPE values were subjected to a one or two-factor analysis of variance (ANOVA) and when appropriate, post-hoc comparisons made by Newman-Keuls test. Results are expressed as mean %MPE $\pm$ S.E.M. for each treatment group. Separate ANOVAs were performed to compare pre- and post-ibogaine/noribogaine baselines for 19 h experiments.

3. Results

The time-course for morphine antinociception revealed a peak effect 30 min after treatment; this decreased with time to a minimum at 120 min (Fig. 1). Ibogaine significantly decreased morphine-induced antinociception when administered 19 h earlier (Fig. 1). The ibogaine-induced reduction was evident at times 60 and 90 min after morphine treatment. In contrast, rats receiving water-saline or ibogaine-saline treatments showed no significant antinociceptive effects. A separate ANOVA of baselines before and after ibogaine pretreatment found no significant differences between the treatment groups.

In contrast to the results of the 19 h ibogaine pretreatment (which decreased morphine antinociception, Fig. 1), co-administration of morphine and ibogaine produced an enhancement of morphine action (Fig. 2). Thus, co-administration of ibogaine and morphine produced higher levels of antinociception and for a longer period of time as compared with the water-morphine group (Fig. 2). Although morphine vehicle groups showed little antinociceptive action after ibogaine, the significant main effect of ibogaine in these experiments (see ANOVA, Fig. 2) suggests the possibility that ibogaine may have slight antinociceptive properties when given alone.

To further explore the ibogaine-induced potentiation of morphine antinociception, the effect of co-administration

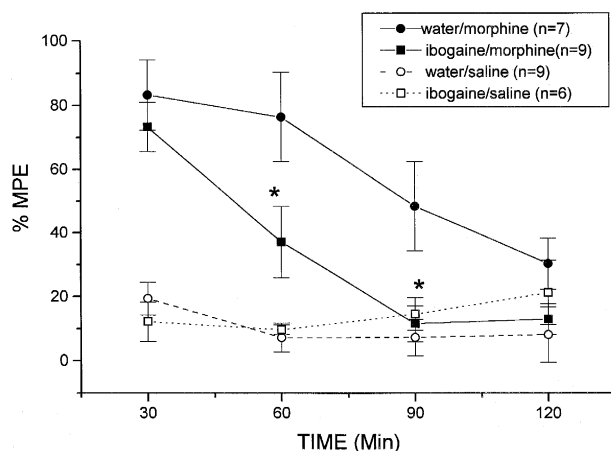


Fig. 1. Modification of morphine-induced antinociception by ibogaine pretreatment (19 h). Rats were tested for baseline nociception prior to receiving ibogaine (40 mg/kg, i.p.) or water vehicle. Eighteen and one half h later, testing was repeated followed by administration of morphine sulfate (4 mg/kg, s.c., neck) or saline. Rats were retested at indicated times (min, abscissa). Antinociceptive scores (% MPE, ordinate, mean $\pm$ S.E.M.) are shown for each group. A two-factor repeated measures (time) ANOVA showed a significant main effect of morphine ($P < 0.01$), but failed to show a main effect of ibogaine ($P = 0.07$), with a significant morphine by ibogaine interaction ($P < 0.02$). Asterisks (*) indicate significant differences for ibogaine-morphine vs. water-morphine treated rats at the same time ($P < 0.05$). A separate ANOVA of baselines before and after ibogaine pretreatment found no significant differences between all treatment groups.

of different doses of ibogaine on morphine antinociception was studied (Fig. 3). As before, the water-morphine group demonstrated a time-course similar to the above experiments (Fig. 3). The figure demonstrates a clear, dose-dependent enhancement of morphine antinociception by ibogaine. The lowest dose of ibogaine administered (1 mg/kg) was inactive at all times.

Since recent reports [8,12] indicate that noribogaine is an active metabolite of ibogaine, the experiments of Figs. 1 and 2 were repeated using noribogaine. When noribogaine was administered 19 h earlier, ANOVA of MPE scores showed a significant main antinociceptive effect of

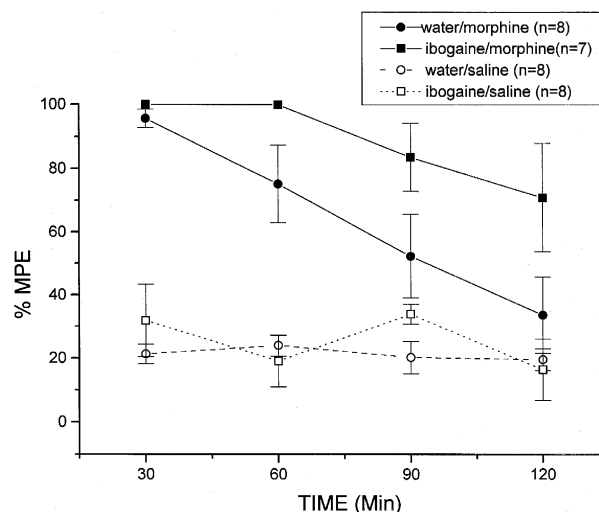


Fig. 2. Effects of ibogaine on morphine-induced antinociception (co-administration). Rats were tested for baseline nociception prior to receiving ibogaine (40 mg/kg, i.p.) and morphine (4 mg/kg, s.c., neck). Drugs were co-administered at time zero, and testing was repeated at the indicated times (min, abscissa). Antinociceptive scores (% MPE, ordinate, mean $\pm$ S.E.M.) are shown for each group. A two-factor repeated measures (time) ANOVA showed significant main effects of morphine, ($P < 0.01$) and ibogaine, ($P < 0.05$). No significant morphine by ibogaine interactions were observed ($P = 0.12$).

noribogaine with no significant morphine by noribogaine interaction. This finding suggests the possibility that noribogaine alone induced an antinociceptive response that was additive with that of morphine (Fig. 4). Since baseline nociceptive scores were measured both before and after noribogaine administration (but both before morphine dosing), a separate ANOVA of these scores was also performed. These results found a significant ($P < 0.05$) 3-way interaction (noribogaine by morphine by time), also suggestive of noribogaine-induced analgesia. However, no significant differences in post-noribogaine (pre-morphine) scores were found between any of the groups by subsequent post-hoc testing, suggesting a borderline effect of noribogaine. When %MPE values were re-computed for

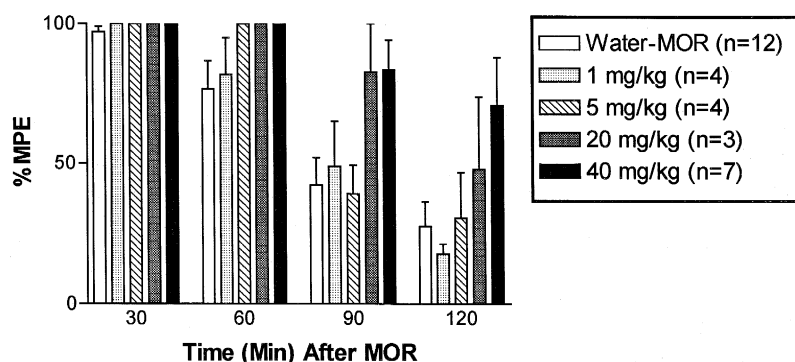


Fig. 3. Ibogaine dose-response curve for morphine-induced antinociception (co-administration). Rats were tested for baseline nociception prior to receiving ibogaine at variable doses (1 mg/kg, 5 mg/kg, 20 mg/kg, or 40 mg/kg, i.p.) or water vehicle. All rats were then dosed with morphine (4 mg/kg, s.c., neck). Drugs were co-administered at time zero, and testing was repeated at the indicated times (min, abscissa). Antinociceptive scores (% MPE, ordinate, mean $\pm$ S.E.M.) are shown for each group. A one-factor repeated measures (time) ANOVA showed a significant main effect of ibogaine ($P < 0.05$).

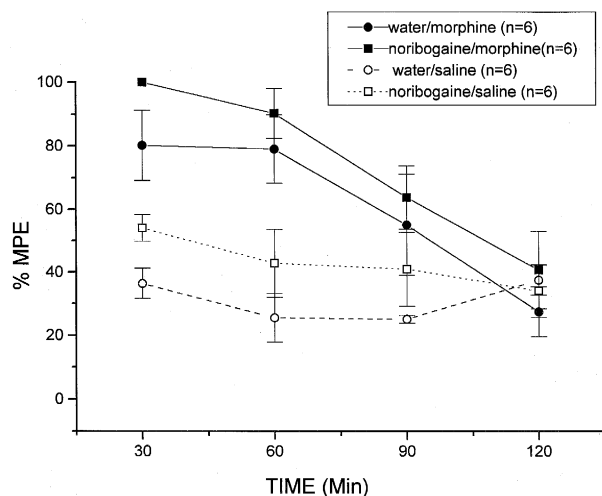


Fig. 4. Modification of morphine-induced antinociception by noribogaine pretreatment (19 h). Rats were tested for baseline nociception prior to receiving noribogaine (40 mg/kg, i.p.) or water vehicle. Eighteen and one half h later, testing was repeated followed by administration of morphine sulfate (4 mg/kg, s.c., neck) or saline. Rats were retested at indicated times (min, abscissa). Antinociceptive scores (% MPE, ordinate, mean $\pm$ S.E.M.) are shown for each group. A two-factor repeated measures (time) ANOVA showed a significant main effect of morphine ($P < 0.01$) and noribogaine ($P < 0.05$). There was not a significant morphine by noribogaine interaction ($P = 0.91$). See text for a discussion of baseline scores.

this experiment using pre-noribogaine baselines (versus post-noribogaine baselines used in Fig. 4) and re-analyzed by ANOVA, the main effect of noribogaine was changed

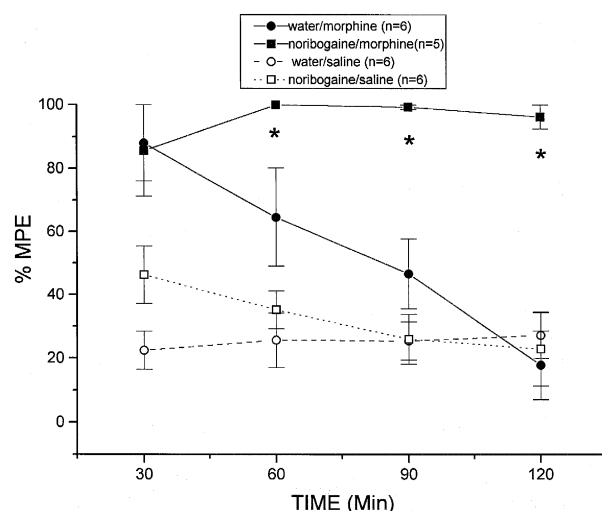


Fig. 5. Effects of noribogaine on morphine-induced antinociception (co-administration). Rats were tested for baseline nociception prior to receiving noribogaine (40 mg/kg, i.p.) and morphine (4 mg/kg, s.c., neck). Drugs were co-administered at time zero, and testing was repeated at the indicated times (min, abscissa). Antinociceptive scores (% MPE, ordinate, mean $\pm$ S.E.M.) are shown for each group. A two-factor repeated measures (time) ANOVA showed significant main effects of morphine ($P < 0.01$) and noribogaine ($P < 0.01$). There was also a significant morphine by noribogaine interaction ($P < 0.01$). Asterisks (*) indicate significant differences for noribogaine-morphine vs. water-morphine treated rats at the same time ($P < 0.05$).

from $P = 0.04$ to $P = 0.09$. Thus, when given 19 h earlier, noribogaine had only slight antinociceptive properties and minimal effects on morphine antinociception.

Interestingly, co-administration of noribogaine and morphine achieved higher levels of antinociception as compared to the water-morphine group (Fig. 5). While the water-morphine group demonstrated a peak effect at 30 min, the noribogaine-morphine treated group exhibited a sustained, near-maximal effect at 60–120 min, significantly different as compared with the respective control groups. A significant morphine by noribogaine interaction was seen (see ANOVA, Fig. 5), consistent with the observed effect.

4. Discussion

The present results are consistent with prior studies investigating the modification of morphine antinociception by ibogaine [5,15]. Hence, when co-administered with morphine, ibogaine increased both the degree of morphine antinociception achieved and the duration of morphine action (Fig. 2). As similar results were obtained in mice [5,15], this ibogaine-morphine interaction appears to be independent of species. However, there have been no previous studies that have examined the impact of 19 h pretreatment with ibogaine on morphine antinociception.

Ibogaine has previously been shown to reduce other effects of morphine. As mentioned, a 19–24 h ibogaine pretreatment decreased both morphine-induced locomotor stimulation [10] and morphine self-administration [9]. The present results show that, like ibogaine's action on morphine's stimulant effects, the 19 h ibogaine pretreatment reduces morphine antinociception (Fig. 1). Thus, opposing effects on morphine antinociception were observed after the same dose of ibogaine was administered at different times. These two opposing actions are likely to be mediated by different mechanisms.

In addition, the present study investigated the potential for noribogaine, an active metabolite of ibogaine [8,12], to modify morphine antinociception. When co-administered with morphine, noribogaine simulated the results obtained with ibogaine-morphine co-administration. That is, both treatments increased morphine antinociception. Moreover, the degree to which noribogaine enhanced morphine antinociception was more pronounced than with the comparable ibogaine treatment (Fig. 5 vs. Fig. 2). This result is consistent with (but does not prove) the hypothesis that noribogaine behaves as an active metabolite of ibogaine. Furthermore, the variability associated with ibogaine action in different subjects might be explained by the reasoning that different individuals could be capable of forming variable degrees of the active metabolite. The 19 h pretreatment experiment with noribogaine showed only a slight (if any) enhancement of morphine antinociception. However, since the 19 h noribogaine pretreatment did not

reduce morphine antinociception, the protracted inhibitory effect of ibogaine remains unexplained.

Several mechanisms could account for the ibogaine-induced modulation of morphine antinociception. One possibility is that ibogaine could change brain levels of morphine by a metabolic drug–drug interaction. For example, the former could inhibit the metabolism of the latter, leading to an increase in blood and brain levels of morphine. However, Glick and colleagues found that a 19 h pretreatment with ibogaine (40 mg/kg, the dose used presently) did not alter brain levels of morphine either 30 min or 2 h after morphine treatment [6]. Thus, the ibogaine-induced inhibition of morphine antinociception observed after a 19 h pretreatment cannot be explained by a metabolic drug–drug interaction. However, no experiments have examined the acute effects of ibogaine on brain morphine levels. Therefore, such a metabolic interaction might explain the ibogaine-induced potentiation of morphine antinociception following co-administration. If so, noribogaine would be expected to induce a similar drug–drug interaction with morphine.

Metabolic drug–drug interactions may not be the only mechanism for explaining the presently observed potentiation of morphine antinociception after co-administration of ibogaine and its metabolite. For example, both ibogaine and noribogaine may be acting by increasing extracellular serotonin levels [12].

Another possibility is that ibogaine could alter morphine receptor or effector interactions. The fact that ibogaine decreases both morphine antinociception and morphine-induced stimulant effects supports the possibility that ibogaine may modify morphine interactions at the mu receptor level [1]. Alternatively, inasmuch as both ibogaine and noribogaine have higher affinities for kappa than for mu opiate receptors [3,13], kappa agonist actions of ibogaine and noribogaine might modulate mu-mediated morphine responses (e.g., [7]).

In summary, ibogaine enhances and inhibits morphine antinociception after acute (0–2 h) and delayed (19 h) administration, respectively. The active metabolite noribogaine may account for the acute effects of ibogaine action. Further studies are needed to determine the mechanism of ibogaine's delayed anti-opiate actions.

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